

REVIEW ARTICLE

Medical and Ethical Studies Cannabis/Marijuana Use Controversy in Indonesia: A Literature Review

Kajian Medis dan Etika Kontroversi Pemanfaatan Ganja di Indonesia: Tinjauan Pustaka

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ABSTRACT

The use of marijuana/cannabis for therapy, especially for certain neurological diseases, is still causing controversy in various countries, including Indonesia. Various studies continue to be carried out while certain parties feel they have the right to get treatment through marijuana based on testimonials and previous research. The urge to legalize the use of marijuana as an alternative therapy is getting tougher, including in Indonesia. Judging from medical ethics, therapy can be applied if its use is following medical indications, the benefits outweigh the risks, its use respects human dignity, and has been clinically tested with scientific research. This research used literature studies from various references to analyze the medical and ethical aspects of using marijuana as a therapy. Potentially Cannabidiol in cannabis can be an alternative therapy, provided that it has passed the correct and ethical scientific research, which is not yet complete. Thus, the legalization of the use of cannabis/marijuana as a therapy still requires stronger and more valid scientific evidence so that the use of cannabis does not reduce human dignity, especially patients as vulnerable people under the pretext of humanity.

Keywords: marijuana/cannabis controversy, marijuana/cannabis legalization, scientific research, medical ethics, human dignity

ABSTRAK

Pemanfaatan tanaman ganja/cannabis untuk terapi, terutama penyakit neurologis tertentu, masih menimbulkan kontroversi di berbagai negara, termasuk di Indonesia. Berbagai penelitian terus dilakukan sementara ada pihak tertentu yang merasa memiliki hak untuk mendapatkan pengobatan melalui ganja berdasarkan testimoni dan penelitian sebelumnya. Desakan untuk melakukan legalisasi pemanfaatan ganja sebagai alternatif terapi semakin keras, termasuk di Indonesia. Ditinjau dari etika kedokteran, suatu terapi dapat diterapkan jika pemanfaatannya sesuai dengan indikasi medis, manfaatnya lebih besar daripada risikonya, pemanfaatannya tetap menghormati martabat manusia, dan sudah teruji secara klinis dengan penelitian ilmiah. Penelitian ini menggunakan tinjauan pustaka dari berbagai referensi untuk menganalisis aspek medis dan etika pemanfaatan ganja sebagai terapi. Potensialnya Cannabidiol dalam ganja dapat menjadi alternatif terapi, asalkan sudah melewati penelitian ilmiah yang benar dan etis, yang sekarang belum paripurna. Dengan demikian, legalisasi pemanfaatan ganja sebagai terapi masih membutuhkan bukti ilmiah yang lebih kuat dan valid agar pemanfaatan ganja tidak justru menurunkan martabat manusia terutama pasien sebagai kaum rentan dengan dalih kemanusiaan.

Kata kunci: kontroversi ganja/cannabis, legalisasi ganja/cannabis, penelitian ilmiah, etika kedokteran, martabat manusia

INTRODUCTION

Cannabis/marijuana or a plant that has the Latin name *Cannabis sativa* is known as a plant from East Asia that pharmacologically contains active phytochemical components such as *tetrahydrocannabinol* (THC) which are known to have psychotropic effects at certain doses, causing a lot of controversies, especially in terms of their intended use. Cannabis was used as therapy in China during the era of Emperor Shen Nung in 2700 BC, in the Middle East as a treatment for seizures around 1800 BC, and in ancient Egyptian civilization to treat pain, vaginal contractions, and various infections. Friedman said that in the early 19th century an Irish doctor named William O'Shaughnessy conducted research on tincture extracts on a 40-day-old baby experiencing nocturnal seizures and working.¹

Until the early 20th century, cannabis research began to be made synthetic, which turned out to reduce the effect of cannabis as an anticonvulsant. These are part of the reasons from several countries consider this plant as a "beneficial" plant and have legalized its use as a therapy.^{2,3}

Currently, several cannabis-derived and synthetic cannabis-related drug products have been accepted by the Food and Drug Administration (FDA), but the use of cannabis as a therapy for certain conditions or certain diseases is still controversial. In Indonesia, cannabis is a type of narcotic class I as defined by WHO, which means it is considered to have addictive effects and is harmful to health, so its use is limited to research that is strictly licensed and is still not permitted to be used as therapy.^{4,5} Requests for legalization of this plant, especially in patients as a treatment therapy for neurological diseases such as *cerebral palsy* and cancer patients, are increasing, this is because the drugs given previously considered were no longer effective for patients. Based on the use of cannabis and several testimonies in previous studies, it also encourages various actions in certain groups to legalize this plant, especially in Indonesia as a medical therapy. There are even families of patients who are pushing the government to legalize the use of cannabis as a therapy for cerebral palsy suffered by their children.⁶ The pros and cons of using cannabis as medical therapy raise a dilemma, especially from a medical and ethical perspective, which is increasingly complex due to Indonesia's communal culture. This article will

explore the benefits and risks of cannabis as medical therapy and consideration of medical ethics to give input and recommendations for the government to decide.

Medical Review of Cannabis as Therapy

Cannabis is estimated to contain 540 compounds of which 100 of them are identified as *phyto cannabinoids*. These compounds are dominated by THC and *Cannabidiol* (CBD).⁷ Currently, a synthetic *cannabinoid* known as *dronabinol* has been discovered.⁸ *Dronabinol* is a THC analog that is currently being developed, one of which is for anti-pain.⁹ However, so far, the Food and Drug Administration (FDA) has only accepted *dronabinol* with indications of nausea, vomiting in chemotherapy and appetite stimulation in AIDS patients.¹⁰

Phytocannabinoids are known to interact with the *endocannabinoid system* via *cannabinoid* (CB) receptors, namely type 1 (CB1) and type 2 (CB2).¹ CB1 receptors are widely expressed in the central nervous system, especially the prefrontal cortex, basal ganglia, hippocampus, amygdala, hypothalamus, and cerebellum. These receptors generate molecular responses related to mood, perception, cognition, and locomotives in humans. Whereas CB2 is expressed in mononuclear cells, especially in macrophages, B cells, and natural killer cells. CB2 receptor activation is thought to be related to the modulation of the immune system. CB2 is expressed quite low in normal neurons and its activation reverses the effect of CB1 activation. Changes in the *endocannabinoid system* are found in several neurological disorders. CB2 is known to be strongly and selectively expressed in microglia in Alzheimer's disease, multiple sclerosis (MS), and *amyotrophic lateral sclerosis* (ALS).¹¹

THC is a psychoactive constituent of *cannabis* and acts as a CB1 and CB2 receptor agonist. THC can activate presynaptic CB1 receptors causing the decreased synthesis of *cyclic adenosine monophosphate* resulting in decreased neurotransmitters.⁸ In animal tests, THC is known to cause catalepsy, *hypolocomotion*, analgesia, hypothermia, and ataxia.¹² CBD is known as the non-psychoactive agent of *cannabis*.⁷ CBD is known to have a low affinity for CB1 and CB2 receptors. Several possible pharmacological mechanisms of CDB have been investigated, but have not been well verified.¹²

Experimental studies show that CB1 and CB2 activation produces beneficial effects in MS models. Administration of CB1 agonists is thought to reduce tremor and spasticity while administration of antagonists exacerbates these conditions, but this study is still in experimental animals. As for clinical studies, *Nabiximols*, which is a combination of THC and CBD, is used as a spasticity therapy in MS but is still an *add-on therapy* and has not been approved by the FDA.¹³ In addition, there was one clinical trial that assessed the effect of *Cannabis sativa L* extract (96% ethanol extraction) with a 2.5 mg THC component compared to a placebo. This clinical trial showed a greater proportion of responses to muscle rigidity in the intervention group, unfortunately, this clinical trial had a *drop-out of >20%* so safety issues became a problem in this study.¹⁴

ALS (*Amyotrophic Lateral Sclerosis*) is known as a degenerative motor neuron disorder for which no cure has been found so far. In this study, an increase in CB2 expression was found in the bone marrow of an ALS animal model, but this animal model is still controversial because the exact cause of ALS is not known.¹¹ This is similar to a postmortem study in ALS patients which also showed CB2 upregulation.¹⁵ Currently the effects of *phytocannabinoids* on ALS are being studied.

In vitro studies show that CBD can modulate the expression of ALS.¹⁶ In animal studies, *nabiximols* have been shown to delay disease progression. Unfortunately, this study was carried out in experimental animal models, which is still controversial for the ALS model.¹⁷ To date, there have been few human studies that have assessed the effects of *phytocannabinoids* on ALS patients. The clinical trial conducted by Weber¹⁸ assessed the effect of THC compared to placebo on the improvement of cramps in ALS subjects, the results showed that there was no significant difference in the improvement of cramps between the two groups. Clinical trials conducted by Riva, et al showed an increase in the Modified Ashworth Scale (MAS) value in the *nabiximols* group.¹⁹ However, this study still has some limitations, including limitations in measuring spasticity, safety issues that may affect results, small sample size, short-term monitoring, and more adverse events in the *nabiximols*.²⁰ Thus, further studies are needed to prove the beneficial effects of *nabiximols* in ALS patients. An ongoing clinical trial namely the EMERALD TRIAL is assessing the effects of CBD in ALS patients. However, based on data from Clinical Trial.Gov, this study has not yet recruited research subjects.²¹

Ethical Review of Cannabis Use as Therapy

Each treatment is aimed at healing or improving the patient's condition while maintaining the methods and processes according to medical moral/ethical standards detailed in the medical code of ethics. Article 6 of the Indonesian Medical Code of Ethics states that treatment that is still in the research stage cannot be claimed to be curative.²² A good motivation, namely helping patients for the sake of humanity, must still pay attention to the rules/laws and ethical principles that apply. If there are side effects that are detrimental to the patient, then even though the doctor's goals/motivations are good, they can ensnare the doctor either in the realm of ethics, discipline, or law.²³ If a doctor prioritizes the patient's interests, then he or she should follow the correct procedure or method. A good goal in health services must be carried out in a good way, as well as with good motivation that underlies its implementation.²⁴ Assessment of whether or not a medical action is ethical is based on the principles of bioethics, especially the principle of respect for autonomy.²⁵

Respect for autonomy emphasizes respect for a person's autonomy or his right to determine what will apply to him. In the context of health services, this right is applied in the patient's approval or refusal of medical action. The patient has the right to choose the medical service he will receive, but that does not mean that this autonomy allows the patient to freely ask the doctor to take the medical action he wants, especially if the action has no indications and the benefits are outweighed by the risks posed to the patient. The existence of this principle requires the doctor to ask for prior approval from the patient as the owner of the body before carrying out a medical action.²⁶ Beneficence means a medical service provided by a doctor must bring optimal benefits according to what is needed by the patient. This principle is active, that is, seeking goodness for patients. Even if the action recommended by the doctor is to postpone or not perform a certain medical action, it is also for the good of the patient who has considered it well that the delay benefits the patient's safety. Beneficence is centered on humans as dignified creatures, whose safety must come first.²⁷ Non-maleficence requires doctors not to commit acts that are detrimental or bring disrepute to patients. Not harming the patient also means taking preventive measures to minimize the risks or side effects that can be caused. Justice is the

principle of applying justice to all patients. As human beings who have the same dignity, every patient also has the same right to get the health services they need, and the same human treatment, regardless of ethnicity, religion, race, etc. These four principles underlie doctor's decision-making in clinical medicine, if a dilemma occurs, then a joint resolution with the patient and family can be pursued by prioritizing the patient's interests.²⁸⁻³⁰

The Dilemma of Cannabis Use as Therapy

Something is said to be in a dilemma if on the one hand, it needs to be done or at least has the potential to be beneficial to do but on the other hand, it contains risks that already exist or has the potential to exist so that the value of the benefits can be doubted.³¹ From an ethical standpoint, a dilemma occurs when there are conflicting or conflicting ethical principles. In the use of cannabis as therapy, several things become a dilemma so good consideration is needed to solve it. Some of the things that give rise to this dilemma are explained as follows:

Table 1. Consideration of the Dilemma of the Use of Cannabis as Therapy

Aspects	Consideration of the positive and benefits	Consideration of negative effects
Ethics (patient rights)	Pantients have the right to choose treatment ²	The doctor has the right to refuse the patient's wishes if they are not in accordance with the principle of medicine ³
Medical	The treatment of chronic neurological disease has shown less than satisfactory result, so new treatment alternative are needed ^{4,5} The positive effects of the substance Cannabidiol have the potential to relieve nervous overactivity	Cannabis as an alternative treatment for chronic neurological disease has not yet fully researched ⁶ The negative neurological effects of THC or other substance in Cannabis/marijuana are not yet fully known, and even worse counter-effects are beginning to be found ⁷
Law	Some countries have legalized the use of cannabis as therapy ⁸	WHO still place cannabis as a class I narcotic that is not suitable for therapeutic use ⁹
Social	They are testimonials of patients who improved after using cannabis therapy ¹⁰ There are activist supporting the legalistion of marijuana who can invite the public to change their perspective on marijuana in the context of medical therapy ^{9,10}	Patients who do not get benefit from cannabis therapy or are negatively impacted by it are not made clear ⁶ The public stigma towards cannabis is still bad as a dangerous substance ¹¹

From this explanation, it appears that several considerations pose a dilemma in the use of cannabis as therapy, a strategy for solving it is needed by analyzing various sides, both medical, social, and ethical.

Recommendations for resolving the ethical dilemma of cannabis use based on an analysis of bioethical principles in the context of Indonesian culture

A dilemma must be solved rationally, by considering various sides to get a solution that is ethical and morally justifiable. In the Indonesian context, cultural considerations greatly influence the decision-making process, so it should also be considered in resolving an ethical dilemma. By using the four principles of Bioethics² that are considered in the context of Indonesian culture, this analysis is obtained on the dilemma of using cannabis as therapy:

Table 2. Analysis of the Ethical Dilemma of Cannabis Use as Therapy (adapted and modified from Beauchamp and Childress)²

<p>Respect for autonomy</p> <ul style="list-style-type: none"> ▪ Patients/families have the right to choose therapy for themselves. ▪ Patients have the right to live better in health. ▪ Patients/families have the right to participate in cannabis research clinical trial by obtaining adequate informed consent. 	<p>Beneficence</p> <ul style="list-style-type: none"> ▪ Cannabis therapy may have good potential for relieving the symptoms of certain neurological diseases. ▪ There were any experiences about the benefit of cannabis. ▪ Further research on cannabis is important for the development of medical science.
<p>Non Maleficence</p> <ul style="list-style-type: none"> ▪ They may be negative effects of cannabis that have yet to be uncovered. ▪ Legalization of the therapeutic use of cannabis has the potential to lead to widespread use of cannabis even for non-therapeutic purpose. ▪ The existence of a negative stigma against cannabis users has the potential to cause negative stigma also for patients who use cannabis therapy which is detrimental to patients psychosocially. 	<p>Justice</p> <ul style="list-style-type: none"> ▪ Patients who have appropriate medical indications have the same right to become participants in cannabis therapy research. ▪ Patients receiving cannabis therapy have the same right to obtain medical services without a certain stigma.

Indonesian Culture:

- Communal culture gives more chances to frame the opinion public about the effects of cannabis from personal experience only than scientific results.

In religious Indonesian culture, using cannabis as a therapy violates religious and human values, which can create a negative stigma for users.



Legalization of cannabis requires scientific as well as cultural and religious studies, involving various parties, medical and non-medical.

According to Table 2 can be seen that from the ethical principle of bringing benefits (*beneficence*) and not harming (*nonmaleficence*), cannabis may have the potential to relieve the symptoms of certain neurological diseases but this is still in the research stage. The significance or not of these benefits is still not finished research. Not all of the negative impacts and risks that can be caused by cannabis are revealed. Thus, the safety of the use of cannabis as therapy is still uncertain.

According to Darby *et al*³², some studies have even found that the positive effects of cannabis are only temporary, and then the user will return to their initial symptoms, even worse (a reverse effect occurs). Other studies even state that the positive effects of cannabis are only subjective effects, which do not have a significant difference from the use of a placebo. This medical consideration becomes difficult when the patient defends his right to receive treatment even though it is still under research, especially with subjective personal experience saying that the therapy he has received is successful, then informing others to form a public opinion that has not been scientifically tested.

With these various considerations, it is too early to make efforts to legalize cannabis as a therapy. Untested safety, efficacy, and the risk of side effects that are not fully known can harm the patient. Against conditions like this, what is needed is not only science education but also a family approach through local leaders. Providing the right education with the right strategy will provide an understanding to the public that patients still have the right to participate in research on the use of cannabis as a therapy without any claims that cannabis has become a therapeutic protocol. This effort must be carried out in synergy with efforts to protect research subject patients from the negative effects of cannabis use. The people's mindset must be straightened out but, in a way, acceptable to the community.³³ Assistance for patients participating in cannabis use research must also be carried out, bearing in mind that the negative stigma is easily obtained by these patients from the community.³⁰

CONCLUSION

The use of cannabis as a medical therapy is still a matter of controversy, especially regarding its ingredients. Several studies have indicated improvement in symptoms in certain neurological patients after treatment with cannabis, but unfortunately, the validity of these studies has not been met. The positive and negative effects of the cannabis plant still require more valid follow-up research such as clinical trials to prove its safety and efficacy aspects as a disease therapy. An ethical dilemma arises because this plant has the potential to be an alternative therapy when there is resistance to previous treatments, but considering the addictive and high return effects, the principles of beneficence and nonmaleficence, in this case, must be thoroughly studied. In addition, the social impact that can arise from the use of cannabis therapy also needs to be considered. The legalization of the use of cannabis as therapy in Indonesia needs to be studied more deeply. Further research is needed on the use of this plant, by paying attention to efforts to minimize the risks or side effects that can be caused to research subjects. These efforts must be carried out with a strategic approach involving community participation.

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AUTHORS CONTRIBUTION

EDAMD designed the study, collected and analysed the data, and wrote the manuscript. JEMHY designed the study, collected and analysed the data, and wrote the manuscript. RM collected and analysed the data, and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no known conflict for this work.

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